# THE MENOPAUSE*

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THE *climacteric* may be defined as that transitional period in women during which cyclic ovarian activity, resulting in menstruation, undergoes cessation. The term *menopause*, strictly speaking, refers to the actual cessation of ovarian activity. The problems arising as a result of this transition extend beyond quiescence of ovarian activity into the *postmenopausal* state. The endocrinological aspects of the problems arising at this period encompass, therefore, all three phases. While generally a spontaneous phenomenon, the menopause may be induced or accelerated by measures which depress ovarian function, such as radiation, or by the removal of the uterus or ovaries, or both.

Although the loss of ovarian secretion is the most important single event and initiates the series of changes which occur at this period, the climacteric must be recognized as a symptom complex involving the readjustment of the whole organism to a new type of internal environment. A change in the balance of the secretion of the ductless glands plays an important part in the reconstruction of this internal environment. Little is known of the exact nature of these changes. That the physiology of the thyroid is at least temporarily altered is apparent from the fact that nodular hyperplasias appear in larger numbers; that this is the age period with the greatest incidence of thyroid atrophy with myxedema; and that the development of Graves' disease is often an accompaniment. A change in the physiology of the pituitary manifests itself in an increased secretion of gonadotropic hormone. The alterations in the other ductless glands accompanying or resulting from the diminution of ovarian activity still remain obscure.

Other biological changes also make their appearance. The climacteric ushers in the decrescent phase of the life cycle of the organism during which the various processes of aging are accelerated and degenerative

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phenomena become correspondingly prominent. These are seen, for example, in the sclerotic vascular changes, in the development of hypertension, and in the degenerative changes in the various viscera and external structures of the body and in the skeleton.

On the psychological level there occurs, likewise, a reorientation of the woman to a new status in relationship to her environment and to her family. Various psychological disturbances ranging from psychoneuroses to the psychoses, of which involutional melancholia is an important example, make their appearance.

The complexity of the menopausal state is apparent and it has only been possible, since the estrogenic hormones have been available, to begin to differentiate between the phenomena due to ovarian insufficiency and those which are part of an even more fundamental rhythm in the life cycle of the species. The chief purpose of this paper is to examine those phases of the menopausal state for which ovarian insufficiency is largely responsible.

The cessation of menstruation at the menopause appears to be a consequence of the gradual aging of the ovary. The Graafian follicles gradually degenerate and disappear, the blood vessels undergo medial thickening with narrowing of the lumen, and fibrosis of the capsule with contraction, occurs. Watson, Smith, and Kurzrok[1] have shown the increasing insensitivity of the human ovary to gonadotropic stimulation with advancing age. The hormonal effect of these degenerative changes is a significant decrease in the production of estrogenic hormone. Concomitant with this is the appearance of gonadotropin of pituitary origin in the urine in far greater amounts than is ever seen during the normal menstrual cycle, during which it can only be detected for brief periods in the course of each cycle. An adjustment must be made to this new hormonal environment of which only these two aspects are known and which must be considered a physiological one for the species. The majority of women manage this successfully; those who are unsuccessful suffer as a consequence a variety of symptoms detrimental to their well-being. No certain knowledge exists as to the physiological influences which promote and those which interfere with this readjustment. Certainly, with respect to the known hormonal changes, there is no detectable difference between the women who adjust successfully and those who fail and we know of no other satisfactory criteria which differentiate between them.

The suggestion has been made that the symptomatology of the menopausal syndrome is due to an excessive production of gonadotropin on the basis of the observation that estrogenic therapy with symptomatic relief is accompanied by a marked reduction in the excretion of urinary prolan. However, Heller and Heller[2] were able to dissociate the symptomatology of the menopause and the concentration of urinary prolan. Their findings are in accord with similar experiments in our laboratory.[3] We must look elsewhere, then, for the factors responsible for this maladjustment.

The treatment of the menopause has made rapid strides in the past few years due to the brilliant work of the chemists who have provided us with specific and powerful estrogenic agents. The problems relating to the climacteric are, however, not solely the province of the endocrinologist and psychiatrist; organic changes in the reproductive tract should not be neglected.

The climacteric may proceed uneventfully and be characterized by a gradual waning of menstrual flow and by cycles otherwise normal. Menstruation may also cease abruptly with no preceding irregularities. Frequently, however, the transition is a stormy period marked by menstrual irregularities, menorrhagias and metrorrhagias which may precede the menopause by many years and offer diagnostic and therapeutic problems. The woman is now entering the age of the greatest incidence of carcinoma, hence such irregularities and bleedings gain significance. One cannot stress too much the desirability for careful gynecological examinations under such circumstances and I feel that it is a necessary precaution to insist that no endocrine therapy be instituted until the gynecologist can assure one of the absence of pathological changes and has corrected any inflammatory lesions, particularly about the cervix, which are felt to predispose towards the development of neoplasms.

## Symptomatology of the Menopause

Symptomatology of the menopause is as bizarre and extensive as any syndrome with which I am acquainted. There are certain classic and well-recognized complaints which are most common and a second group of signs and symptoms which occur less frequently but are apparently specifically related to this state. Among the most common symptoms are the vasomotor, with the characteristic hot flush followed by drenching sweats, and the dizziness, palpitation and exhaustion which follow

the attacks. There are also the disturbances of peripheral circulation which take the form of paresthesias and numbness. Insomnia is frequently complained of and asthenia may be profound enough to prevent the patient from carrying out her duties, both domestic and social. In addition, there are a variety of gastrointestinal symptoms largely of functional character. One of the most uncomfortable complaints is of headache. Arthralgias and degenerative changes in various joints contribute to the picture. Changes are noted in the texture of the skin and subcutaneous tissues. Occasionally such phenomena as urticaria and angioneurotic edema are seen. With time, senile atrophic changes occur in the genital tract with attendant discomfort. In many patients there is a definite tendency to gain weight and to become aware of fat deposits different from those seen in early life. On the behavior level, the woman tends to become depressed, emotionally unstable, irritable and given to weeping. She is inclined to withdraw more and more into herself, feel insecure and become hypochrondriacal, resentful and suspicious. Other psychoneurotic manifestations may make their appearance or be exaggerated. The sexual life may wane in intensity although occasionally this period is associated with increasing sexual interest. Frank psychoses may be initiated.

Although these symptoms, which could easily be supplemented by many others, generally make their appearance on the cessation of menstruation, they are frequently seen during the period of transition. At this time it is not uncommon for them to be more marked premenstrually when estrin production is at its lowest and to improve or disappear with the development of the ovarian follicle during the first half of the cycle when the production of estrin is increased.

## Choice of Therapeutic Agents in the Treatment of the Menopause

The proper therapeusis of any disturbance of the ductless glands is dependent on the availability of specific secretions of the glands involved and on objective methods to guide their use. The first of these criteria is fulfilled with respect to the secretions of the ovary. At present there are available three estrogenic hormones of known chemical structure and potency. These are estrone, which is the ketohydroxy estrin; estradiol, the dihydroxy estrin; and estriol, the trihydroxy estrin. Differing widely in their estrogenic activity by weight, equivalent results can be

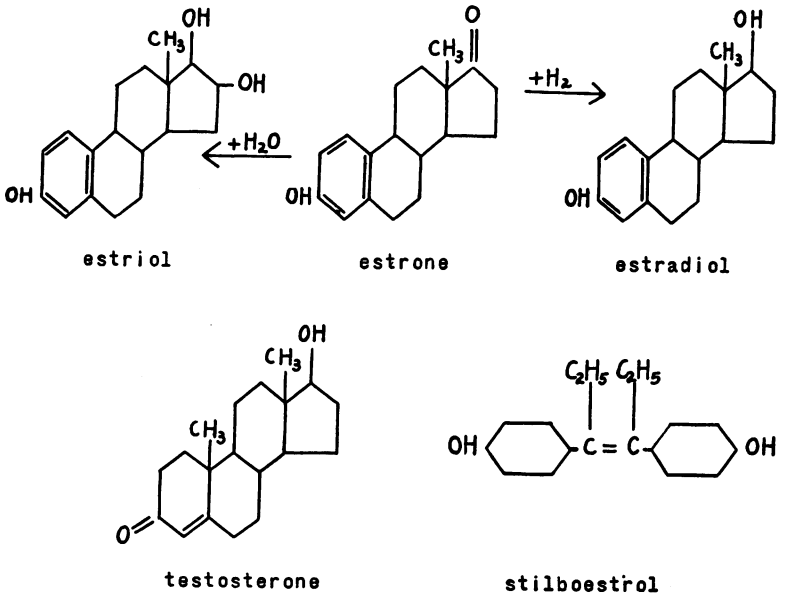


Fig. 1—Hormones used in treatment of the Menopausal Syndrome.

obtained with all, provided adequate amounts are administered. I have found estrone and estradiol to be the most effective and economical for replacement therapy in the human. Estriol preparations are designed for oral administration and should prove equally useful once they are made available at reasonable cost in sufficient potency. Estradiol is usually conjugated with either benzoic or propionic acid in an effort to prolong its activity. These estrogens are standardized in terms of rat and international units, the rat unit being derived from biological assay usually according to the method of Allen and Doisy. On the basis of their biological assay in the human, we have come to rely on the activity expressed in rat units, as the various estrogenic preparations we have analyzed have corresponded to each other in potency rather better on the basis of the rat unit than on the international unit. In addition to the natural estrogenic compounds, two synthetic estrogens have been employed, stilbestrol and ethinyl estradiol; and, interestingly enough, the androgenic hormone, testosterone, conjugated with propionic acid, has proved itself an agent capable of ameliorating menopausal symptoms.

The second criterion, objective methods for the applications of these therapeutic agents, has also been fulfilled to a large extent. Several

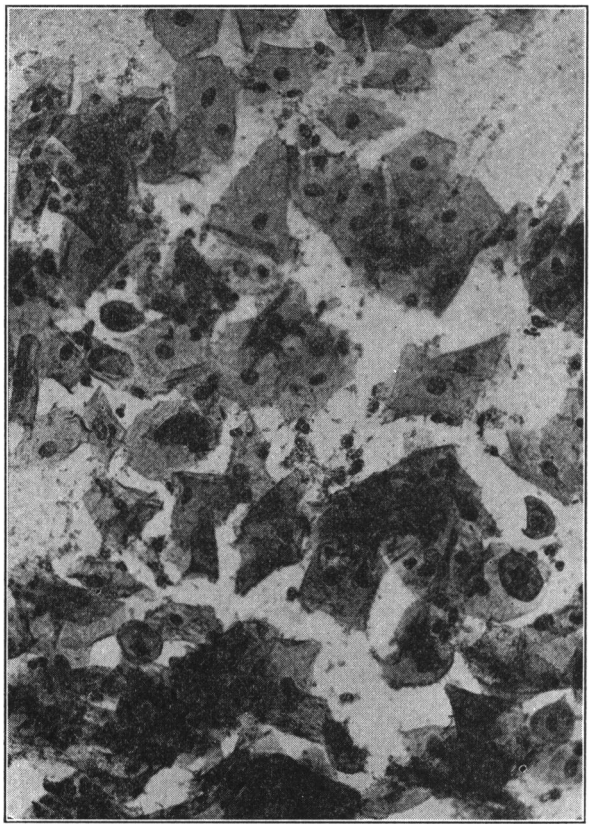

Fig. 2—A characteristic menopausal smear prior to treatment with estrogens. Note small oval "deep" cells, undifferentiated squamous cells with large nuclei, cell clumps, bacteria, smudgy appearance, and absence of cornified cells.

possible indices can be employed. It has been suggested that, since the estrogens reduce the initially high titer of urinary gonadotropin of the menopause, the disappearance of this hormone from the urine might serve as an index of full replacement therapy. The disadvantages inherent in the use of this method are that it is laborious and still far from exact. Furthermore, the appearance and disappearance of urinary prolan in relation to symptomatology[2] and vaginal smear changes[3] have been found to be inconstant and unreliable. The estimation of an elevation of the estrin level in the urine following replacement therapy is also a laborious and time-consuming procedure. Endometrial biopsies to detect

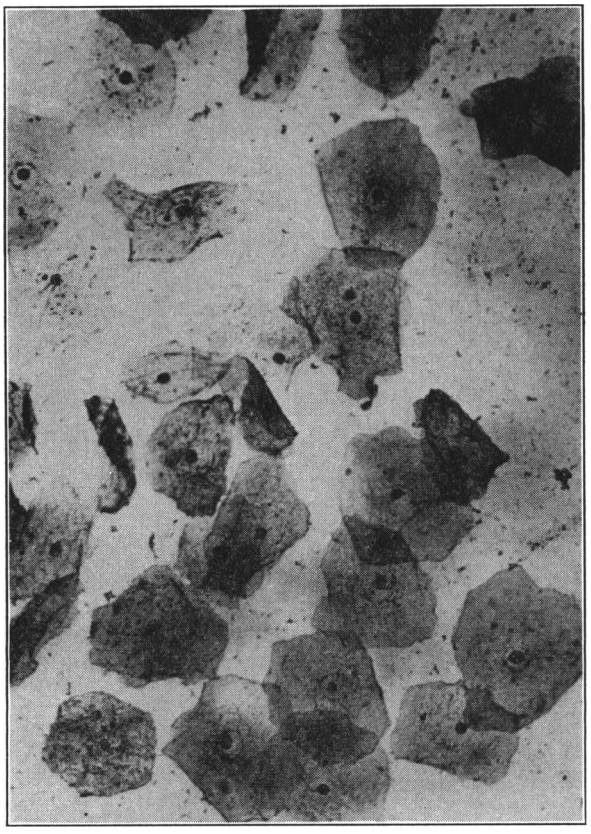

Fig. 3—Follicular vaginal smear after estrogenic therapy. Note that all cells are typically cornified, with small pyknotic nuclei, discretely arranged in a clear field free of debris. This represents the peak effect of replacement therapy with estrogenic hormones. When this smear picture is attained, all symptoms due to ovarian insufficiency per se should disappear. (Papanicolaou and Shorr, Reference 4.)

estrogenic effects are associated with trauma and are inconvenient to obtain with any frequency.

In 1935,[4] the vaginal smear was introduced as a method for evaluating the effect of estrogenic hormonal therapy in the human. During the menopause, as a result of the low estrin production, the vaginal epithelium undergoes considerable atrophy. The desquamated vaginal secretion, when aspirated by a simple glass pipette, placed on a slide and stained, reflects faithfully the state of the vaginal epithelium. During

the menopause, it presents a typical picture, quite different from that seen during the normal menstrual cycle. It is free of cornified cells, the squamous cells are of the intermediate type and there are varying numbers of small, round or oval cells from the deeper layers of the epithelium. Bacteria, leukocytes, cellular debris and occasionally red blood cells are to be seen. The smear presents a "smudgy" or "dirty" appearance. When estrogens are given in adequate amounts a series of changes takes place in the smear until it is transformed into one similar to that seen mid-menstrually in the normal cycle. This induced follicular phase is characterized by the presence of cornified cells which are usually discrete, by the absence of leukocytes and debris, and by a clear appearance. At this stage, which represents the peak effect of estrogenic therapy, all of the symptoms due to ovarian insufficiency per se should disappear whereas those of other origins will persist.

This method has the virtue of simplicity, specificity and the absence of trauma. In addition, it can be repeated as frequently as desired. By its use in man it has been possible to assay biologically the variety of estrogenic compounds available and to set up standards for their use. We had hoped by this method to arrive at a definite biological unit for man which would represent a full replacement dose just as the rat or mouse unit is equivalent to an estrogenic unit in these rodents. Had this been possible the therapy of the menopause would have been greatly simplified. We found, however, that individual patients varied greatly in the amount of hormone necessary to produce an equivalent biological effect. Though the "human" unit lay between 2,000-3,000 R.U. daily for most patients, a spread of as much as 1000 per cent, as from 1,000 to 10,000 R.U. daily, was observed. Therefore, as regards dosage, each patient becomes an individual problem.

It also became apparent that menopausal symptoms in different patients were not uniformly sensitive to estrogenic therapy. In about one-fourth of the patients symptomatic relief occurred with relatively little change in the vaginal smear; with about one-half, relief was experienced at intermediate levels; and with the remainder, complete relief was not obtained until full replacement and a follicular smear were achieved. With this, as well as all other objective indices employed, there is apparently no absolute correlation with symptomatology. The smear does, however, have particular value in dealing with the variety of bizarre menopausal symptoms, especially those of a psychoneurotic character,

since by insuring complete estrogenic replacement, it permits a differentiation between those complaints specifically due to ovarian insufficiency and those arising from other causes.

Given effective therapeutic agents and objective methods for guiding their use, we must now consider how best to apply them to the problems presented by the menopausal syndrome. There are two major therapeutic objectives, one is to abolish the complaints which result from failure to adjust to the new status; the other, to achieve as rapidly as possible a satisfactory adjustment which will free the patient from further need of such exogenous support. This program must deal with questions of dosage, the modes of administration as regards effectiveness, convenience and economy, the possible dangers of neocarcinogenesis, the influence of therapy on the eventual readjustment, and the problem raised by the effects of estrogen on the endometrium.

To some of these questions there are fairly satisfactory answers. To others, our present incomplete knowledge permits of no final conclusions.

Much can be said with certainty as to the choice of preparations and the modes of administration. Those estrogenic agents which have proved effective in man have been discussed above. The choice of the mode of administration is largely an economic problem. Estrogens are at present generally employed by the intramuscular route because this is the least expensive. They are also effective by mouth but as they lose so much of their activity by this route, from 10 to 20 times the parenteral dose must be given to obtain the same estrogenic effect. This loss of efficiency by mouth should be kept in mind when transferring from the parenteral route, and it would be desirable to have all estrogenic preparations designed for oral administration standardized in terms of actual activity corrected for this loss of potency. One such preparation is so labelled. The topical application of estrogens in pessary form for the discomfort associated with senile vaginal changes is the accepted method of dealing with this condition. In addition to these routes, Bishop[5] and Salmon, Walter and Geist[6] have introduced crystals of estrogenic hormone subcutaneously. This has proved economical and effective by virtue of the slow absorption of the crystals, and the action of the estrogen has been greatly prolonged. It will be of interest to see whether such prolonged action on the endometrium will result in bleedings which cannot be well controlled. This has apparently occurred in 4 of 20 patients treated with

implants by Twombley.[7] This problem does not exist in the absence of the uterus. The final choice will undoubtedly be the oral route once the cost of estrogens is lowered. One such estrogen, stilbestrol, which is very effective by mouth and is inexpensive, has been synthesized and has aroused great interest because of these properties.

Questions relating to dosage and the best methods for regulating therapy cannot as yet be answered with similar definiteness. Our relatively brief experience with estrogenic agents has not as yet permitted the recognition of the best principles on which to base a therapeutic regime. The wide variations from patient to patient in the subjective and biological response to estrogens make any attempt at standardization of dosage futile. There is likewise no general agreement as to the extent of symptomatic relief to be aimed at. An equal uncertainty exists as to which regime is best adapted to permit the hoped-for readjustment to the menopausal status.

The regime adopted in this Clinic may be briefly set forth with full appreciation of what may prove to be its shortcomings. It is based on the control of hormonal therapy by means of the vaginal smear rather than on subjective symptoms alone. Following a pelvic examination to rule out organic disease, and a psychological evaluation, the patient is placed on graded doses of an estrogen until a full follicular phase is reached. This represents complete replacement therapy. The first course of treatment extends over 4 to 5 weeks during which a correlation is made between the degree of smear change and the extent of subjective relief. This permits the observer to judge the sensitivity of the individual response to the estrogen, the level of dosage and the smear change at which optimal effects occur, and the character of the symptoms for which ovarian insufficiency is specifically responsible. One is frequently struck by the greater well-being which can be achieved in this way than when subjective indices such as the flush are relied upon exclusively. The results of this first course of therapy serve as a guide for further management.

Treatment is then interrupted. The speed and intensity with which symptoms recur enable one to form an opinion as to the severity of the syndrome and the probable ease or difficulty of the eventual readjustment. The second purpose of the rest period is to permit the regression of the induced endometrial hyperplasia in order to avoid the discomfort of bleeding from a too-prolonged uterine stimulation. Bleeding

will, however, occasionally occur and its significance should be made clear to the patient.

Treatment is resumed after a two-week interval if the return of symptoms warrants it. The dosage and level of the smear which afford optimal relief is now selected. Excessive dosage is thus avoided and the full benefit inherent in the therapy realized. The response of the patient to this regime is extremely variable. With favorable cases, each succeeding course finds optimal symptomatic relief achieved with progressively smaller doses until the need for further support ceases entirely. In the unfortunate, large doses may be required for many years with little or no evidence of an impending readjustment. All stages between these extremes are seen. Along with the hormonal therapy every effort is made to deal with other factors which may contribute to the persistence of symptoms. Of most value in this respect is the psychotherapeutic approach.

The problems involved in spacing the treatment deserve brief comment. Where oral administration is possible, it is most efficient to give the hormone daily. When the intramuscular route is employed the inconvenience of daily injections is usually an obstacle to the maintenance of an even concentration of hormone in the body. It can be shown by studies of the vaginal secretion that the more widely spaced the less efficient are injections of estrogens even if conjugated with benzoic or propionic acid. The practice of giving large doses of estrogen at long intervals is not only inefficient but carries with it whatever dangers may be inherent in the marked and repeated shifts in the histology of the endometrium change it induces. In the hysterectomized patient this difficulty does not exist but the possible effects on the breast must be borne in mind in relation to malignancy.

Concern has been expressed lest intensive estrogenic therapy delay the eventual readjustment. This has led many workers to recommend that the dose be just that which allows the patient to be comfortable and that it be steadily and systematically reduced with a view to assisting the readjustment of the post-menopausal status. This regime may prove satisfactory for some patients but for the most part I have been unsuccessful in accelerating readjustment by such an enforced reduction in dosage. It is my impression that estrogenic therapy per se does not interfere with the eventual transition and that there is little reason to withhold the full benefit inherent in these therapeutic agents.

This chapter would be incomplete without reference to the management of menopausal symptoms arising during the climacteric prior to cessation of menstruation.[8] These symptoms are occasionally as severe as those seen at the menopause. While they may occur throughout the cycle, they are more commonly present premenstrually and during the flow, disappearing with the increased estrin production of the developing ovarian follicle. They respond equally well to replacement therapy. When they occur premenstrually they are best treated by the administration of estrin from the mid-point of the cycle up to a few days before the expected flow. When they occur at menstruation the flow need be no contraindication to the administration of estrogen, in the absence of pelvic disease. Not infrequently it serves to reduce the excessive flow which may occur in the climacteric. The dose on the first and second day should be relatively small, for example, about 500 R.U., and may be raised on the succeeding days until the symptoms disappear. It is often helpful when symptoms occur during menstruation to administer the hormone for a short period premenstrually as well. When symptoms occur throughout the cycle, estrin should be administered throughout. As at the menopause, no standard dosage can be prescribed. The average patient experiences relief with 1,000-2,000 R.U. three times weekly except for a 3 to 4 day period prior to the expected flow, but here again each patient presents an individual problem.

*The Synthetic Estrogen, Stilbestrol*

This interesting therapeutic agent, diethyl-stilbestrol, was synthesized by Dodds and his associates in 1938.[9] As may be seen from its formula, it differs from the natural estrogens in that it does not contain the phenanthrene-ring system formerly thought to be necessary for estrogenic activity.

It was found to be an extremely powerful estrogenic agent in animals, suffering little diminution in potency by the oral as compared to the parenteral route. It reproduced virtually all the effects of the natural estrogens in animals and was about two and one-half times as active as estrone by injection. By mouth, its superiority over the natural estrogens was even more striking. It will be recalled that the natural estrogens, estrone and estradiol, like the thyroid hormones, are effective by mouth. However, about 15 to 20 times the parenteral dose must be administered orally to produce the same effect, as judged by vaginal

smears. Stilbestrol, on the other hand, lost half or less of its activity by mouth. These attributes, its high estrogenic activity, its oral efficiency, and its cheapness, gave promise of a wide usefulness in human therapy. Preliminary experiments on animals had indicated that it was devoid of toxic activity.

The first reports of its clinical use were highly favorable.[10,11] Stilbestrol reproduced all the effects observed with the natural estrogens, including the relief of menopausal symptoms. More extensive clinical studies, while confirming its estrogenic properties and attendant relief of symptoms, brought out certain undesirable side reactions chiefly referred to the gastrointestinal tract, and consisting of nausea, vomiting and anorexia. Also evidence began to accumulate from toxicity studies that its use in animals was sometimes followed by damage to various tissues, especially the liver.

Our own experience with stilbestrol[12] was derived from a study of a series of forty-four women, two of whom had primary amenorrhea, in whom estrogenic activity was the chief point of interest, and forty-two with the menopausal syndrome, who permitted an evaluation of its effects on symptoms. The estrogenic effects were followed by vaginal smears and biopsies. The therapeutic goal in each patient was the induction of a full follicular smear as well as symptomatic relief. The results of our study may be briefly summarized as follows.

We could confirm the previous observations that stilbestrol is a powerful estrogenic agent losing little of its potency by mouth and capable of ameliorating subjective symptoms of the menopause. The oral estrogenic unit for the human was found to lie between 2 mg. and 4 mg. daily.

Its use, however, was associated in our series with a high percentage of toxic symptoms in the form of nausea, vomiting, abdominal distress, anorexia, diarrhea, lassitude, paresthesias, vertigo, thirst, and skin rashes. There appeared to be no relation between the size of the dose and the development of toxic reactions; nor was there evidence of an acquired tolerance to the drug. The side effects appeared to be largely central in origin since they followed injection as well as oral administration. Liver function tests were inconclusive.

The incidence of side effects in the group of patients studied was a good deal higher than other workers have reported. Their existence, however, whatever the incidence, certainly warrants caution in the use

of this preparation and our feeling is that, until the nature and significance of the toxic effects are understood, it should be regarded as an experimental preparation.

One is tempted to speculate on the nature of the toxic results obtained with stilbestrol. It is of interest that the two synthetic estrogens, stilbestrol and ethinyl estradiol, have this in common, that they are both very potent by mouth and both produce the same type of toxic side reaction. The explanation for the loss of potency of the natural estrogens by mouth is held to be their degradation during passage through the liver. This organ has been shown to have the capacity to destroy natural estrogens by some still obscure process. The synthetic estrogens apparently escape this degradation in the liver. At least such an explanation would account for their oral potency. Such a mechanism may function to prevent the accumulation of estrogens in the circulation above levels which are adequate for their effects on the structures they specifically influence. An excessive accumulation in the blood stream might have an unfavorable effect on other structures in the body. We may well be witnessing with stilbestrol those undesirable effects which are prevented with the natural estrogens by this mechanism of neutralization. The greater oral potency of stilbestrol may therefore be gained at the expense of the safety of the organism.

*The Male Sex Hormone in the Menopause*

The history of the use of male hormones in disturbances of female sex physiology is an interesting one. The existence of both hormones side by side in both sexes still awaits a full explanation. Animal experiments in which the balance between estrogens and androgens has been altered artificially, have afforded some clues. The first effect observed was an inhibition of the pituitary with a subsequent suppression of the estrous cycle; the second was a neutralization of the peripheral effects of estrogens on the secondary sex structures. A similar type of action has also been found in man. Loeser[13] first demonstrated the atrophic effects of androgens on the endometrium in women and pointed out its use in dealing with excessive bleeding. Studies from this laboratory[14] showed that human menstruation could be suppressed at will with androgens, to return when treatment was stopped. We were also able to demonstrate a peripheral antagonism between the male and female sex hormones in the case of vaginal epithelium.[15] The ratio of

androgen to estrogen, necessary to produce this effect, was about 50 to 1. This is far greater than the excretion ratio of these hormones in women. Hence the estrogenic influence predominates. In man, therefore, the same types of effects were to be observed as in animals—an inhibitory effect on the pituitary with subsequent suppression of menstruation, and peripheral neutralization of estrogens by androgens.

What was quite unexpected was that androgens should be capable of abolishing the symptoms of the menopause, although one property was common to both types of hormones, i.e., the ability to depress the excretion of urinary gonadotropic hormones of pituitary origin.[16] That the androgens were indeed capable of ameliorating the symptoms of the menopause became apparent from the work of Salmon[16] and others as well as from our own studies.[15] The effective dose was rather high, in the neighborhood of 25 mg. daily. The use of androgens in the menopause had one advantage; it was unassociated with any withdrawal bleeding, since its effect on the endometrium is to induce atrophy rather than hyperplasia.

However, disadvantages soon became apparent in the form of increased hirsutism, enlargement of the clitoris, and a lowering of the voice, unpleasant sequelae which often take a long time to reverse themselves. When one considers the duration of replacement therapy in the menopause, it becomes apparent that this symptomatic effect of the androgenic hormone, while of interest to the student of sex physiology, does not justify its use as a substitute for the natural estrogens.

## Estrogens and Carcinoma in Man

One of the deterrents to the widespread use of estrogens in man has been a consequence of animal experiments demonstrating the capacity of these hormones to produce carcinoma under certain conditions. It is not yet clear whether the carcinogenic effect of the estrogens is direct or dependent on the release of genetic predispositions on the part of these animals. Whatever the explanation, there has been considerable concern over the possible effects of the extensive use of these hormones on the incidence of carcinoma in the human.

Conditions under which carcinoma is produced in animals differ in certain important respects from those under which the estrogens are ordinarily used in human therapy. Carcinoma is most readily induced in strains of animals having a high incidence of spontaneous carcinoma.

The amount of estrogen administered has been very large in proportion to the weight of the animals. Furthermore, the hormones must be given over a large part of the life span of the animals.

In humans it is impossible to assay the innate tendencies towards carcinoma; the duration of therapy is relatively short and the dose of estrogens ordinarily employed is physiological, approximating the quantity elaborated in the normal economy of the organism.

This problem cannot be approached as directly in man as in animals, for one cannot deliberately seek to bring about the production of carcinoma in man except under unusual circumstances. We are, therefore, forced to evaluate the significance of estrogenic therapy in the human by analyzing the incidence of new growths in large series of cases in which the hormones were used for a sufficient length of time to make this evaluation significant. Other methods of approach take the form of studies of the histological changes in the uterus after prolonged therapy.[17,18]

We have analyzed a series of 452 cases treated with estrogens during the past seven years at the New York Hospital.[19] Most of these patients were treated by a similar regime, making them a relatively uniform group. Every precaution was taken to minimize factors which might predispose towards carcinogenesis. Prior to any treatment, thorough pelvic examinations were made and any inflammatory lesions found were corrected because of the relationship between chronic inflammation and carcinoma. Repeated gynecological check-ups of the state of the pelvis were made and the breasts carefully examined for the presence of nodules. The therapeutic use of the hormones was controlled by means of vaginal smears, permitting full replacement therapy to be achieved in most of the patients and the avoidance of excessive doses. No patient, therefore, received at one time more than would be equivalent to one human unit. This is far lower than the amounts needed to produce carcinoma in animal experiments. Thirdly, the estrogens were given with as short an interval as feasible between doses in order to avoid the irregularities of endometrial hyperplasia and regression which might be favorable conditions for neoplastic changes. In patients with an intact uterus, treatment was interrupted every four to six weeks to allow for a regression of the endometrial hyperplasia and to avoid a too prolonged stimulation.

An analysis of this group of 452 cases shows that at least in one

respect it fulfilled the conditions of the successful animal experiments, namely, a high tumor population. There were 82 cases of benign myomata of the uterus with removal prior to treatment, and one carcinoma of the fundus, also removed prior to treatment. Ninety-eight ovaries were removed, all benign; and there were nine mastectomies, three for malignant neoplasms. Of this group, one woman, who had a bilateral mastectomy in 1934 with the finding of an adenocarcinoma in one breast, developed metastatic lesions and a recurrence of the breast tumor four years after the original operation. She had received in this interval 3,000,000 I.U. of estrogen. The recurrence within this time does not warrant the conclusion that the estrogenic therapy was responsible. Otherwise the series was free of any instances of development of neoplasm. This, in conjunction with other studies cited, appears to offer no support for the view that the use of the estrogenic hormones in man is associated with the danger of neocarcinogenesis, provided therapy is carefully controlled in the manner indicated.

### Results from Estrogenic Therapy in the Menopause

Since the signs and symptoms which present themselves at the menopausal age are part of a complex situation in which ovarian insufficiency is but one of the etiological factors, it becomes of importance to try to ascertain what effects may be expected from the use of hormones alone. In this way we obtain a better sense of proportion as to the significance of the whole set of changes at this life period. For those symptoms and signs which are not corrected by replacement therapy, other approaches must be sought or they must be accepted as inevitable consequences of the decrescent period of the life cycle.

The classical symptoms of the menopause, such as the vasomotor crises, headache, asthenia, insomnia, and the disturbances of peripheral circulation, may be expected to disappear at various levels of replacement therapy. Some of these, such as the hot flush, disappear more rapidly than others and are not too good subjective criteria on which to guide dosage. Pushing therapy to full replacement is the most certain method of determining the degree of well-being which can be experienced. No more gratifying restoration of health can be achieved in therapeutics than is so frequently seen in the menopause under adequate treatment.

Too much, however, must not be expected as regards many signs

and symptoms which accompany this syndrome but which are apparently part of a more fundamental alteration characteristic of this age period. One of the most troublesome complaints is that of joint pain involving particularly the knees, spine, and hands, and occasionally most of the other joints. It is an osteoarthritis of degenerative character, and seems to be specifically associated with the climacteric. Obesity tends to accentuate the difficulties. Hall[20] has reported considerable relief of these symptoms with estrogenic hormones. Our experience agrees with his in that, on the whole, the arthralgias are benefited. They may nevertheless persist, and frequently severely, despite intensive estrogenic therapy. They appear to belong to the group of degenerative changes in this age period the progress of which can be only partially influenced by ovarian hormone therapy.

There is some difference of opinion as to whether the hypertension so often seen at the menopause is specifically influenced by estrogenic therapy. Analysis of our results indicates that a well-stabilized hypertension is scarcely, or not at all, influenced by hormonal therapy. Where marked variations in blood pressure are encountered in association with emotional instability, the tension may be expected to be stabilized at the lower levels when estrogenic therapy has reduced the vasomotor instability and emotional tension. Nor does the obesity of this period seem to have any specific relation to the ovarian insufficiency. It should be dealt with by those measures which are employed at other ages, with, however, an avoidance of drastic procedures.

The anticipation that the estrogens would function as sex hormones in the sense that they would be able specifically to influence libido, has not been realized. There is a growing awareness that the sexual drive is grounded in more fundamental factors and that the concept that it was solely dependent on the reproductive secretions was an oversimplification of an extremely complex and subtle reaction. The changes in libido at the menopause are inconstant and to a large extent dependent on the intensity of the previous sexual drive and on the general discomfort attendant on the menopausal syndrome. The most that should be expected from replacement therapy is that libido be restored to its premenopausal level. The few instances where libido is increased are attributable to non-hormonal influences which enter the complex picture of this age period.

The psychic disturbances so prominent at this age period present an

involved picture which make it necessary to discriminate in terms of the character of the disturbance. The ability of a woman to survive the menopause without serious emotional disturbance is an indication of her previous emotional stability. A large proportion of the women who seek relief from menopausal symptoms have been maladjusted for a long time prior to the onset of the menopause. The majority of these women have presented psychoneurotic symptoms of the neurasthenic and hypochondriacal type. With the additional stress of the menopause these symptoms become accentuated. In addition, there are likely to be symptoms of anxiety and tension.

If there has not been serious maladjustment of the psychoneurotic type, the menopausal symptoms such as the depression and emotional instability are rather promptly relieved by hormonal replacement therapy. On the other hand, if the psychoneurotic maladjustment has been marked, there is usually only partial relief or relief of a temporary character, and some form of psychotherapy is necessary.

A smaller group of patients have more deeply seated problems such as may be noted in introverted or schizoid personalities. These patients tend to develop chronic hypochondriacal complaints, and sometimes the clinical syndrome of involutional melancholia. It would appear that, in the involutional cases, the menopause acts as a factor in precipitating a psychotic reaction which had for some time been latent and which represents a combination of personality problems for which there is no apparent solution. Feelings of guilt because of tabooed sexual thoughts or practices, or the resentment over the realization that the sex life is in part terminated, impose a burden to which the woman is unable to adjust.

An optimistic view with respect to the therapeutic benefit of estrogenic therapy in the psychotic reactions of the menopause has been expressed by several groups of workers, particularly Werner and his associates,[21] who have reported very favorable results with estrogens in involutional melancholia. Our more pessimistic attitude is based on a study of a small series of cases carried out with Ripley and Papanicolaou[22] in the Payne-Whitney Clinic of the New York Hospital. Of these, twenty were intensively studied for long periods. Seven were instances of involutional melancholia, six fell into the manic-depressive group, seven were milder reactions of a more reactive nature which may be classified as psychoneuroses of the depressive type. Full replace-

ment therapy, controlled by vaginal smears, with far larger doses than those employed in the previous studies cited was given for long periods during hospitalization.

Our general conclusions were that no specific effect on the psychosis could be expected from estrogenic therapy. Wherever associated menopausal symptoms contributed to the discomfort of the patient, these symptoms could be abolished. With this improvement in the general well-being of the patient came a somewhat better ability to cope with their problems, but this aid was of a non-specific character.

## Problems Still Presented by the Menopausal Syndrome

Despite the gratifying progress that has been made in the treatment of the menopausal syndrome, many questions still remain unanswered. The situation is somewhat analogous to Graves' disease and diabetes mellitus where a therapeutic measure of considerable effectiveness still leaves unsolved many of the primary problems relating to the genesis of the disease.

Of the questions still awaiting solution, one may be singled out for brief comment in concluding this survey because of my growing conviction that it may reach to the heart of the problem. Our therapeutic successes should not cause us to lose sight of the fact that we have no knowledge of the cause of the menopausal syndrome. We believe that it represents a failure to adjust to the new internal environment which follows the cessation of ovarian function; but why this occurs in one group of women and not in the other remains obscure. When one studies the menopausal syndrome from the broader aspects of the evolution of the total personality, it becomes increasingly apparent that here as well as in Graves' disease, psychogenic factors may play a very important, if not primary, role in preventing an adjustment to the new status. One sees instances in which the adjustment to the menopause had taken place smoothly years before, and where acute and distressing symptoms suddenly arose years afterwards in association with some emotional stress. One sees relief of menopausal symptoms following therapy with an apparent satisfactory adjustment suddenly interrupted by a renewal of all the old complaints in their original intensity under the influence of some new psychic strain. The importance of psychic influence is also commonly seen in the greater resistance of the severely psychoneurotic menopausal patient not only to the subjective but to

the biological effects of estrogenic hormones.

The implications of these observations for the direction of our future approach to the study of the problem of the menopause are apparent. The sooner we learn to regard the menopausal syndrome not as an entity but as a symptom of a more fundamental psychobiological maladjustment, the more rapid will be the attainment of our eventual therapeutic goal, its prophylaxis.

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